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A Randomized Controlled Phase IIb Trial of Beta$_1$-Receptor Blockade for Chronic Degenerative Mitral Regurgitation

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Objectives The purpose of the study was to evaluate the effect of long-term β_1-aderergic receptor (AR) blockade on left ventricular (LV) remodeling and function in patients with chronic, isolated, degenerative mitral regurgitation (MR).

Background Isolated MR currently has no proven therapy that attenuates LV remodeling or preserves systolic function.

Methods Thirty-eight asymptomatic subjects with moderate to severe, isolated MR were randomized either to placebo or β_1-AR blockade (Toprol-XL, AstraZeneca, London, United Kingdom) for 2 years. Magnetic resonance imaging with tissue tagging and 3-dimensional analysis was performed at baseline and at 6-month intervals for 2 years. Rate of progression analysis was performed for endpoint variables for primary outcomes: LV end-diastolic volume/body surface area, LV ejection fraction, LV end-diastolic (ED) mass/ED volume ratio, LV ED 3-dimensional radius/wall thickness; LV end-systolic volume/body surface area, LV longitudinal strain rate, and LV early diastolic filling rate.

Results Baseline LV magnetic resonance imaging or demographic variables did not differ between the 2 groups. Significant treatment effects were found on LV ejection fraction ($p = 0.006$) and LV early diastolic filling rate ($p = 0.001$), which decreased over time in untreated patients on an intention-to-treat analysis and remained significant after sensitivity analysis. There were no significant treatment effects found on LV ED or LV end-systolic volumes, LV ED mass/LV ED volume or LV ED 3-dimensional radius/wall thickness, or LV longitudinal strain rate. Over 2 years, 6 patients treated in the placebo group and 2 patients in the β_1-AR blockade group required mitral valve surgery ($p = 0.23$).

Conclusions β_1-AR blockade improves LV function over a 2-year follow-up in isolated MR and provides the impetus for a large-scale clinical trial with clinical outcomes. (Molecular Mechanisms of Volume Overload-Aim 1 [SCCOR in Cardiac Dysfunction and Disease]; NCT01052428) (J Am Coll Cardiol 2012;60:833–8) © 2012 by the American College of Cardiology Foundation

Degenerative mitral valve disease, usually related to mitral valve prolapse, is responsible for most cases of isolated mitral regurgitation (MR) in the United States (1). There is no effective medical therapy for isolated MR, and therefore, surgery is recommended in patients with severe MR and symptoms or evidence of progressive left ventricular (LV) dysfunction (2,3). The natural history of MR is progressive LV dysfunction and adverse LV remodeling, eventually leading to heart failure. Initially, LV dilation and augmented stroke volume occur, facilitated by an increase in preload and by ejection into the relatively low-pressure left atrium. These changes are accompanied by increased sympathetic drive early in MR in both animal models (4,5) and humans (6). However, prolonged excessive adrenergic stimulation has a cytotoxic effect on cardiomyocytes (7), resulting in

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Abbreviations and Acronyms

AR = adrenergic receptor
BSA = body surface area
CI = confidence interval
3D = 3-dimensional
ED = end-diastolic
EDV = end-diastolic volume
EF = ejection fraction
ESV = end-systolic volume
LV = left ventricular
MR = mitral regurgitation
MRI = magnetic resonance imaging

increased LV end-systolic dimension or volume and wall stress. In the canine model of isolated MR, chronic β_1-adrenergic receptor (AR) blockade has been shown to improve cardiomyocyte and LV function (8,9). In patients with severe MR and normal LV ejection fraction (EF), β-AR blockade is associated with a survival benefit with or without coronary artery disease (10).

In humans with moderate to severe degenerative MR, 14-day treatment with β_1-AR blockade decreases LV work, but with increases in LV end-diastolic volume (EDV) and end-systolic volume (ESV) and no change in LV EF (11). However, the beneficial effect of β_1-AR blockade on LV function in heart failure is achieved after long-term therapy, and there has not been a human trial of extended β_1-AR blockade on LV remodeling and function in patients with isolated MR. Therefore, the current randomized, controlled study used magnetic resonance imaging (MRI) with tissue tagging and 3-dimensional (3D) analysis as a surrogate outcome to evaluate the effects of long-term β_1-AR blockade on LV remodeling and function in patients with chronic, isolated MR.

Methods

Study population. Eligible patients had moderate or severe MR documented by color flow Doppler, LV EF of more than 55%, LV end-systolic dimension of <40 mm, and echocardiographic thickening of the mitral valve leaflets and prolapse. Patients were excluded with New York Heart Association functional class III or IV symptoms, previous myocardial infarction, significant coronary artery disease by exercise testing with myocardial perfusion imaging, significant other valvular disease, serum creatinine level of more than 2.5 mg/dl, and hypertension requiring medical treatment. The study was approved by the University of Alabama Institutional Review Board, and all subjects gave written informed consent.

Study protocol. We conducted a randomized, double-blind study with 2 years of treatment of β_1-AR blockade with Toprol XL (AstraZeneca, London, United Kingdom) (range: 25 to 100 mg/day) versus placebo in patients with moderate to severe MR. Toprol XL was administered with a starting dose of 12.5 to 25 mg/day and was titrated as tolerated at 2-week intervals to a maximum of 100 mg/day. After randomization, patients underwent MRI scanning, which was repeated at 6, 12, 18, and 24 months after randomization. MRI also was performed in control volunteers (mean age: 52 ± 11 years, range: 35 to 70 years) who had no prior history of cardiovascular disease and were not taking any cardiovascular medications.

Cardiac MRI. As previously described (12,13), MRI was performed on a 1.5-T MRI scanner (Signa GE Healthcare, Milwaukee, Wisconsin) optimized for cardiac application. The short axis volumes defined by the contours, excluding papillary muscles, were summed to calculate LV volume (12,13). LV volume-time curves were constructed and differentiated with respect to time to obtain peak diastolic filling rates (13).

Three-dimensional LV geometric parameters were measured from surfaces fit to endocardial and epicardial contours manually traced near end-diastole and end-systole. 3D wall thickness was computed by measuring the perpendicular distance from a point on the endocardial surface to the closest point on the epicardial surface.

Tagged MRI scans were acquired with repetition times of 8 ms, echo times of 4.4 ms, and tag spacing of 7 mm. 3D LV strain was measured from tagged images at end-systole, which was defined by visual inspection of the image data as the time frame with maximum contraction (14). Two-dimensional strain rates were measured using harmonic phase analysis (15), which measures local myocardial 2-dimensional strain based on the local spatial frequency of tag lines. Strain and strain rates were computed at each segment in the American Heart Association 17-segment model and were averaged over the mid-ventricular segments.

Statistical analysis. PRIMARY OUTCOME VARIABLES. Analyses of MRI scans were performed blinded and side by side in 1 sitting for each patient. MRI outcome variables were categorized according to the following: 1) LV geometry: LV end-diastolic volume (EDV)/body surface area (BSA), LV ED mass/LV EDV, 3D LV ED radius/wall thickness (midwall); 2) LV systolic function: LV EF, LV ESV/BSA, 2-dimensional LV systolic longitudinal strain rate; and 3) LV diastolic function: LV peak early filling rate (EDV/s).

ANALYSIS. The *t* test (for continuous variables) and Fisher exact test (for categorical variables) were used to compare demographic characteristics, clinical characteristics, and outcome variables at baseline between the 2 groups. Treatment differences in the rate of progression, assessed on an intention-to-treat basis, was the focus of the comparisons over time between the treatment groups. Rate of progression for each outcome was modeled with SAS PROC MIXED (SAS Institute, Cary, North Carolina) assuming the best working correlation structure based on the Bayesian information criterion from the choices of autoregressive lag 1, heterogeneous autoregressive lag 1, compound symmetry, and heterogeneous compound symmetry. Compound symmetry was found to be the best structure for all outcomes except for LV EDV/BSA, where autoregressive lag 1 was found to be the best structure. A significant interaction effect between the linear component of time and the

treatment group was the measure of treatment effect, assessed at $p < 0.05$.

MRI examinations were performed at 6-month intervals over the 2-year study period. To achieve a more accurate representation of a patient's rate of progression over time, the actual time of the MRI relative to randomization that is closest to a 3-month interval (i.e., 0, 3, 6, 9, 12, 15, and so on) was used in the analysis, instead of the target 6-month visit. For example, if a patient was scheduled to have a 12-month MRI but actually underwent an MRI examination 2.5 months late from the target visit, the time associated with the MRI data for this visit was considered to be at 15 months, instead of 12 months.

Results

Demographic data. Demographic data are summarized in Table 1. Thirty-eight patients were enrolled: 19 in the placebo group and 19 in the Toprol group. One patient in the placebo group dropped out soon after the randomization, and 1 patient in the Toprol group died of pulmonary embolus after cosmetic surgery shortly after the 12-month visit. Thus, 36 patients had 2 years of follow-up data. However, these patients were included in the random effects models on an intention-to-treat principle.

Baseline age, sex, race, heart rate, or blood pressure did not differ between groups. Of the 38 MR patients, 10 had holosystolic murmurs, with 5 in treated patients and 5 in untreated patients. No patients had a flail leaflet. No patients had atrial fibrillation, and all patients were New York Heart Association functional class I or II, with 90% and 95% of placebo and treatment groups being in New York Heart Association class I, respectively.

Table 1 Baseline Demographic and Clinical Characteristics of Patients with Isolated Mitral Regurgitation

Variable	Placebo	Toprol	p Value
N	19	19	
Female	9 (47%)	11 (58%)	0.7459
White race	19 (100%)	16 (84%)	0.2297
Age (yrs)	56 ± 9.2	52.9 ± 9.1*	0.3101
Systolic blood pressure (mm Hg)	121 ± 14	125 ± 14	0.3859
Diastolic blood pressure (mm Hg)	75 ± 11	75 ± 8	0.8905
Heart rate (beats/min)	67 ± 12	66 ± 11	0.8238
NYHA functional class I	17 (90%)	18 (95%)	~1.0000
MRI variables			
LV EDV/BSA (ml/m^2)	92 ± 17	96 ± 20	0.4964
LV ED mass/LV EDV (gm/ml)	0.61 ± 0.13	0.61 ± 0.12	0.9720
LV ED radius/wall thickness	4.76 ± 0.92	4.69 ± 0.92	0.8001
LV EF (%)	63 ± 5	62 ± 6	0.7820
LV ESV/BSA (ml/m^2)	34 ± 7	36 ± 8	0.4258
Peak systolic longitudinal strain rate (%/s)	88 ± 27	83 ± 29	0.5619
Peak early filling rate (EDV/s)*	2.27 ± 0.61	2.12 ± 0.57	0.4139

Values are n (%) or mean ± SD. *Peak early filling rate (milliliters per second) normalized to EDV.
BSA = body surface area; EDV = end-diastolic volume; ESV = end-systolic volume; LV = left ventricular; ED = end-diastolic; EF = ejection fraction; MRI = magnetic resonance imaging; NYHA = New York Heart Association.

At baseline, MR patients had 35% higher LV EDV/BSA, 50% higher LV ESV/BSA, 33% higher LV stroke volume/BSA, and 18% lower LV ED mass/EDV ratio, whereas LV EF was slightly lower in MR patients versus control subjects (Online Fig. 1, Online Tables 1 to 4).

Analyses of outcomes. First-order and second-order polynomials for time effects were fitted for all outcome variables, and coefficients associated with the second-order terms were not found to be significant. Therefore, a first-order (linear) time effect model was used. Figures 1, 2, and 3 display the raw data by treatment group for each LV outcome with the fitted lines as well as the fit with 95% confidence bands based on individual confidence intervals for the means at each time point. Table 2 displays the estimates and standard errors for the annual rates of progression (slope × 12 months) for each group including the p values, which compare the estimates between the 2 groups.

There were no significant treatment effects found on LV EDV/BSA ($p = 0.457$), LV ED mass/EDV ($p = 0.1967$), or LV ED 3D radius/wall thickness ($p = 0.55$). Significant treatment effects were identified on LV EF ($p = 0.006$), whereas no significant treatment effects were found on LV ESV/BSA ($p = 0.214$) or LV systolic longitudinal strain rate ($p = 0.16$). The slope of LV EF per month for the Toprol group was estimated to be 0.04 (95% confidence interval [CI]: −0.08 to 0.16, not significantly different from 0), whereas the slope of the placebo group was estimated to be −0.21 (95% CI: −0.33 to −0.08, significantly different from 0, $p = 0.001$). This implies that the LV EF for the placebo group after 2 years is expected to decrease by as little as 1.92% and as much as 7.92%, on average, with 95% confidence. Significant treatment effects were detected for LV diastolic function measured by the peak early filling rate from the MRI volume time curves ($p = 0.001$). The slope for the Toprol group was estimated to be 0.008 (95% CI: −0.002 to 0.017), whereas the slope for the placebo group was estimated to be −0.015 (95% CI: −0.02 to −0.005). In addition, there was a treatment effect for heart rate ($p = 0.006$) and systolic blood pressure ($p = 0.03$) in the placebo group versus the Toprol-treated MR patients (Online Fig. 2).

Sensitivity analyses. Sensitivity analyses were performed to account for a possible effect in the statistical analyses of participants who had undergone mitral valve surgery. These patients are identified (black lines) in Figures 1, 2, and 3. Surgery is performed because it is expected that the patient's condition will improve. Therefore, it is logical to assume that the data observed after surgery of the patients who underwent mitral valve repair or replacement is better than what it would have been if they did not undergo surgery; hence, the data after surgery were replaced with the worst value for the visit within the treatment group. The conclusions were the same.

Adverse events. Although generally there was a pattern of a higher adverse event or serious adverse event frequency in the placebo group, by design the study was not powered to

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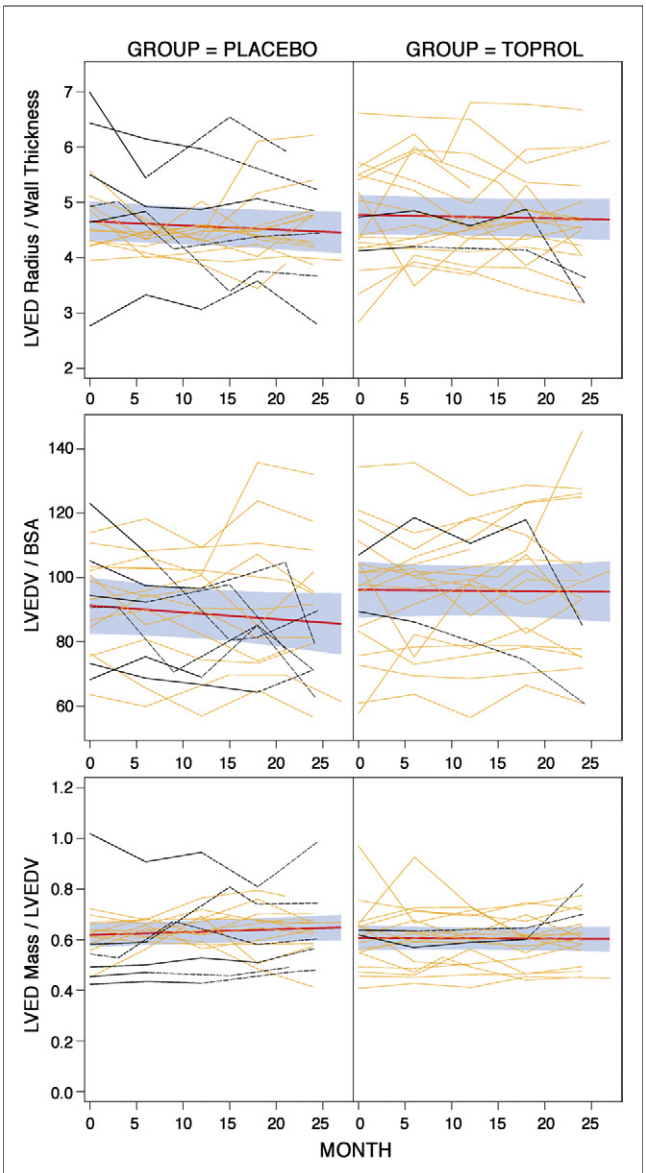

Figure 1 **Changes in Left Ventricular End-Diastolic Volumes and Geometry Over 2 Years**

Treatment efficacy is shown by the difference in rates of progression **(slopes of the red lines)** between the placebo and Toprol groups. The **blue-shaded area** represents the 95% confidence intervals for the mean outcome at a given time point. Individual patient data over time are shown for those with surgery (**black solid lines** before surgery and **broken lines** after surgery) and without surgery **(yellow)**. There was no treatment effect for left ventricular (LV) end-diastolic volume (EDV)/body surface area (BSA), LV ED mass/LV EDV ratio, or LV ED 3-dimensional radius/wall thickness.

detect modest differences between groups. Twelve of the 19 patients randomized to placebo and 8 of the 19 patients randomized to Toprol experienced at least 1 adverse event. Seven of the 12 in the placebo group and 3 of the 8 in the Toprol group experienced serious adverse events. A formal test of the hypothesis using the Fisher exact test did not show this difference to be statistically significant ($p = 0.33$ for adverse event and $p = 0.27$ for serious adverse event). Six of the 19 patients in the placebo group and only 2 of the 19 in the Toprol group had undergone mitral valve repair or replacement. The Fisher exact test also did not show this difference to be statistically significant ($p = 0.23$).

Discussion

In this randomized placebo-controlled study, chronic β_1-AR blockade prevented the progressive decline of LV EF, whereas LV EF slope decreased in the placebo group. At randomization, all patients were within standard echocardiographic guidelines, with an LV end-systolic dimension of less than 40 mm and an LV EF of more than 55% in the absence of symptoms. The beneficial effects of β_1-AR

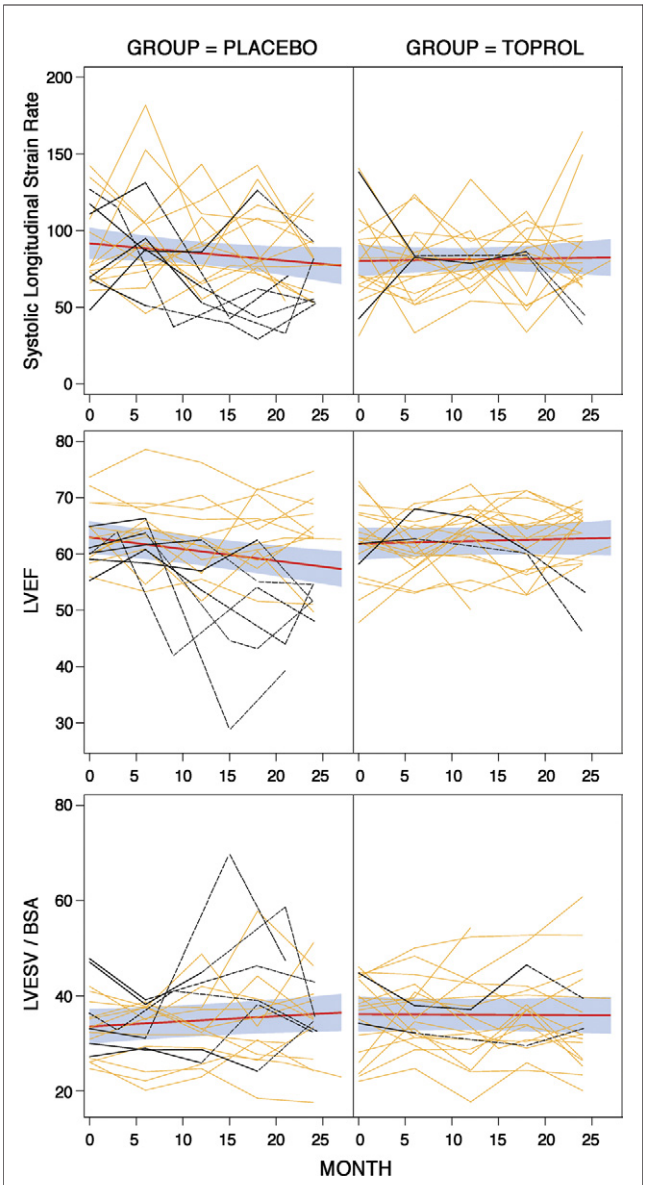

Figure 2 **Changes in LV Systolic Function Over 2 Years**

There was a significant treatment effect for LV ejection fraction (EF), but not for LV end-systolic volume (ESV)/BSA or LV peak systolic longitudinal strain rate. (See Fig. 1 for details.) Abbreviations as in Figure 1.

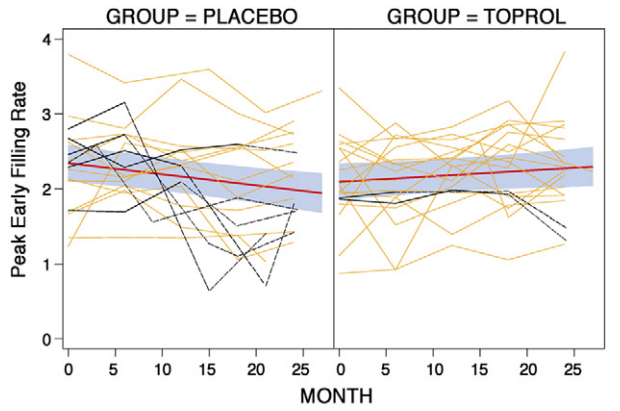

Figure 3 **Changes in LV Diastolic Function Over 2 Years**

There was a significant treatment effect for peak early left ventricular (LV) diastolic filling rate. (See Fig. 1 for details.)

blockade persist on an intention-to-treat basis and with a sensitivity analysis. There is no difference in the rate of progression for systolic wall stress calculated using blood pressure and 3D radius/wall thickness at the base, mid, or distal LV (data not shown). Thus, the tendency for an increase in LV ESV in the placebo group resulting in a decrease in the slope of LV EF may represent a decrease in contractility. In parallel with the effects on LV systolic function, early LV diastolic filling rate demonstrates a decreasing slope in placebo and an increasing slope in treated patients.

No treatment effects were detected for LV remodeling. The discordance between LV remodeling and improved LV systolic function with β_1-AR also has been reported in the canine model of isolated MR (8,9). The dog model of isolated MR is marked by loss of extracellular matrix components essential to cardiac geometry (16,17), decrease in protein synthesis (18), and decrease in profibrotic growth factors, including transforming growth factor-β (16). Thus, extracellular matrix loss combined with a less robust hypertrophy response produces LV wall thinning and a decrease in LV EDV mass/volume ratio (16,17), as in our MR study patients (Online Tables 1 to 4). These myocardial responses are a poor match for antifibrotic and antihypertrophic effects of renin-angiotensin system blockade, which explains why this therapy or vasodilators do not attenuate LV remodeling in isolated MR (2,3). Although β_1-AR blockade improves LV and cardiomyocyte function in the MR dog, interstitial collagen loss is unchanged, which may explain the failure to attenuate LV dilatation (9).

β_1-AR blockade exhibits a trend toward preventing the need for operative intervention; however, the current study is not powered adequately to evaluate this outcome. Of interest, Figure 1 demonstrates baseline MRI-derived LV EF of less than 55% in 3 patients who received β_1-AR blockade. The discrepancy between echo-derived LV end-systolic dimension and fractional shortening and MRI volume-based LV EF likely resides in the mid and apical spherical remodeling distal to standard echo-derived LV end-systolic dimension at the tips of the papillary muscles (19). Online Figure 1 and Online Tables 1 to 4 demonstrate the greater amount of LV apical spherical remodeling, which contributes to increased LV ESV. Nevertheless, LV EF slope was positive in the treated group, further supporting the beneficial effect of β_1-AR blockade in isolated MR.

We do encourage caution that spurious findings may have arisen from the multiple statistical tests conducted for the 7 outcomes considered in this report. Because this was a pilot study, it was not clear at the inception what adjustments were appropriate to protect from the possibility of these spurious findings. However, even the most conservative approach, a Bonferroni adjustment with alpha of 0.0071 (0.05/7), subsequently was shown not to affect the interpretation of the findings, because all factors significant at 0.05 also were significant at this strict level. In addition, as noted in the statistical methods, multiple correlation structures may be used to analyze the data. The choice of an appropriate structure was based on a priori and objective criteria of goodness-of-fit indices for the model using that particular working correlation and were not based on treatment differences in the outcome measures. Thus, it is worth noting that using autoregressive structures considered or using actual times when MRI was undertaken resulted in no significant differences in any of the outcomes.

The current study uses cardiac remodeling as a surrogate outcome to assess the potential beneficial impact of β_1-AR blockade in chronic isolated MR. Although we are convinced that the surrogate outcome of LV EF will be related strongly with important clinical outcomes, including prevention of heart failure and prolonging the need for surgical intervention, the current study does not definitively establish that clinical outcomes will improve, an association that can be assessed only in a Phase III randomized clinical. Nevertheless, this study using LV functional outcome, in

Table 2 **Estimated Annual Rates of Progression (Increase if Positive and Decrease if Negative) of Each Outcome for Each Treatment Group**

Outcome Variable	Slope Estimates (SE)		p Value
	Placebo	Toprol	
LV EDV/BSA (ml/m^2)	−2.53 (2.19)	0.25 (2.14)	0.4568
LV ED mass/LV EDV (gm/ml)	0.01 (0.01)	−0.00 (0.01)	0.1967
LV ED radius/wall thickness	−0.09 (0.06)	−0.04 (0.06)	0.5550
LV EF (%)	−2.48 (0.75)	0.47 (0.75)	**0.0060**
LV ESV/BSA (ml/m^2)	1.31 (0.81)	−0.11 (0.81)	0.2144
Peak systolic longitudinal strain rate (%/s)	−6.48 (3.70)	0.96 (3.73)	0.1587
Peak early filling rate (EDV/s)*	−0.18 (0.06)	0.09 (0.06)	**0.0011**

*Peak early filling rate (milliliters per second) normalized to EDV. p Values are for comparing the estimates for the groups.
Abbreviations as in Table 1.

addition to other reports of a survival benefit in patients with isolated MR (10), provides empiric support for the use of β_1-AR blockade in patients with chronic degenerative MR. These findings call for a large multicenter clinical trial to confirm these effects.

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Key Words: beta blockade ■ medical therapy ■ mitral regurgitation ■ mitral valve disease.

APPENDIX

For supplemental tables and figures, please see the online version of this article.